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Anti–Methicillin-Resistant *Staphylococcus aureus* (MRSA) Cephalosporins Plus Daptomycin as Initial Therapy for MRSA Bacteremia: Does a "Hit Hard and Fast" Strategy Improve Outcomes?

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Background. The study aim was to evaluate the effectiveness of anti–methicillin-resistant *Staphylococcus aureus* (MRSA) cephalosporins in combination with daptomycin (anti-MRSA Ceph + DAP) compared to other antimicrobial regimens (OARs) as initial treatment of MRSA bloodstream infection (BSI).

Methods. This retrospective observational study enrolled patients with MRSA-BSI from 1 January 2020 to 31 December 2024 at 4 large Italian hospitals. The primary endpoint was 90-day all-cause mortality. Cox regression was used for primary endpoint analysis; results were confirmed with inverse probability of treatment weighting (IPTW). Treatment efficacy was also assessed using the desirability of outcome ranking (DOOR) approach, assigning 1 additional point beyond recovery for 1 of the following negative outcomes: (*i*) persistent MRSA infection, (*ii*) persistent bacteremia (≥5 days), (*iii*) drug resistance, (*iv*) any adverse event, and (*v*) 90-day relapse. A score of 7 was assigned for death at any time point.

Results. Overall, 465 patients were enrolled: Median age was 76 (IQR, 61–83) years, 59% male, with a Charlson Comorbidity Index score of 7 (IQR, 4–8). Of them, 50 (11%) and 116 (25%) patients had endocarditis and metastatic infection, respectively. Importantly, 90-day mortality occurred in 181 (39%) patients, while 260 (56%) experienced at least 1 negative outcome included in DOOR analysis. Overall, patients in the anti-MRSA Ceph + DAP arm had a 59.9% (95% CI, 52.4%–67.4%) probability of having a better outcome than those in the OAR arm. Particularly, anti-MRSA Ceph + DAP was associated with reduced mortality (aHR, 0.54 [95% CI, .34–.85]), confirmed after adjustment with IPTW analysis.

Conclusions. Anti-MRSA Ceph + DAP could represent a valid initial therapy for MRSA-BSI, especially in patients with high risk of worse outcomes.

Keywords. MRSA-BSI; combination therapy; mortality; treatment failure.

Staphylococcus aureus bloodstream infection (BSI) is one of the leading infectious cause of morbidity and mortality, with reported attributable mortality rates ranging from 15% to 30% [1, 2]. Among different bundle interventions [3], the initial antibiotic therapy is still debated; regarding methicillin-resistant *S. aureus* (MRSA) BSIs, current guidelines indicate vancomycin (VAN) or daptomycin (DAP) monotherapy [4].

Nevertheless, monotherapies with DAP or VAN are often associated with persistent bacteremia and high rates of treatment failure, especially in severe infections [5]; consequently, alternative regimens, including VAN- or DAP-based combination therapies, potentially associated with higher in vitro killing properties, are suggested in case of refractory MRSA-BSI [6].

Several studies explored the safety and effectiveness of alternative strategies over monotherapies; combinations of VAN/DAP with β-lactams [7, 8] or DAP plus fosfomycin [9] are the most studied recently. However, results are conflicting due to high heterogeneity of population of study and different timing of combination therapy initiation, leaving these strategies with no clear place in therapy.

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Furthermore, anti-MRSA cephalosporins such as ceftaroline (CPT) and ceftobiprole (BPR) have emerged as other potential alternatives due to their potent bactericidal activity, with noticeable in vitro antibacterial synergy with DAP [10].

Currently, monotherapy with anti-MRSA cephalosporins is supported as treatment of MRSA-BSI alternatively to DAP [11, 12], but preliminary clinical data suggest that combining anti-MRSA cephalosporins plus DAP may exert a higher bactericidal activity, especially in early phases of BSI, producing a faster clearance of bacteremia [13–15]. However, what advantages this microbiological activity confers in clinical practice remains uncertain, and the place in therapy of anti-MRSA cephalosporins plus DAP combination over standard monotherapy remains a matter of debate [16].

Herein, the effectiveness of initial treatment with anti-MRSA cephalosporins plus DAP for MRSA-BSI is evaluated, if compared with other antimicrobial regimens (OARs).

METHODS

Study Design

This was a retrospective observational multicenter study conducted at 4 Italian centers: Policlinic of Bari; Policlinic of Bologna "Sant'Orsola-Malpighi"; Humanitas IRCCS Hospital, Rozzano (Milan); and Centro Cardiologico Monzino, Milan, between 1 January 2020 and 31 December 2024.

The centers included share the same standard of care of *S. aureus* BSI management, described in Supplementary Data 1.

Study Population and Inclusion/Exclusion Criteria

All patients with MRSA-BSI were included. Demographic data, medical history, clinical, microbiological, and treatment data were collected for each patient.

Inclusion criteria were age ≥18 years; ≥1 positive blood culture for MRSA associated with clinical signs/symptoms of infection; and initiation of targeted therapy within 48 hours of positive index blood culture with at least 1 anti-MRSA regimen.

Exclusion criteria were death within 48 hours of targeted treatment initiation or before receiving any effective therapy; absence of follow-up blood cultures; or lack of data regarding treatments or outcomes.

Definitions used in the manuscript are shown in Supplementary Data 2.

Primary and Secondary Outcomes

The primary endpoint was the 90-day all-cause mortality from BSI onset.

Secondary endpoints were as follows: (*i*) treatment failure to first-line antibiotic therapy; (*ii*) 30-day all-cause mortality; (*iii*) 90-day relapse or persistence of infection signs at any site; (*iv*) median duration of bacteremia after targeted treatment initiation; and (*v*) treatment-related adverse events (including *Clostridioides difficile* colitis).

The follow-up was completed for all patients with medical assessment, telephonic interview, and/or based on municipal records database (mortality). Mortality was evaluated using information from hospital records that were linked with a municipal records database. Our hospital information system allows us the access to patient personal data (living or deceased status, date of death).

Desirability of Outcome Ranking

A desirability of outcome ranking (DOOR) approach has been performed, to better understand the global impact of anti-MRSA cephalosporins plus DAP treatment strategy versus OARs [17].

Outcomes were assessed with DOOR with 7-ordinal ranking, and it was based on current available literature [17, 18]. The score was prespecified before the analysis. One point was assigned to every single outcome, and a rank was obtained from 1 to 7, with 1 as the most desirable outcome and 7 the worst outcome (death):

- 1 point for infection cure at the end of follow-up (day 90).

Plus 1 additional point for each of the following:

- Persistent clinical signs of MRSA infection, defined as unchanged or worsened Sequential Organ Failure Assessment (SOFA) score or admission to intensive care unit (ICU) after at least 7 days of effective treatment.
- Persistent bacteremia for ≥5 days.
- Development of drug resistance to at least 1 molecule during therapy (defined as a MRSA strain with an antibiotic shifting from susceptible to resistant).
- Any adverse events of grade 3 or 4 (including *C. difficile* colitis), according to Common Terminology Criteria for Adverse Events (CTCAE).
- 90-day infection relapse.

Statistical Analysis

Descriptive Statistics and Survival Analysis

The objective of the study was to compare clinical outcomes for patients receiving different antibiotic regimens. A flowchart of inclusion of patients and analysis structure is provided in Supplementary Figure 1.

Continuous variables were presented as median with interquartile range (IQR); count and percentage described the categorical variables. Categorical variables underwent comparison with $\chi 2$ test or Fisher exact test, as appropriate. The Wilcoxon rank-sum test was employed for continuous variables. The independent impact of variables on survival was assessed through both unadjusted and multivariate-adjusted hazard ratios (HRs) using Cox proportional hazards regression. Adjusted hazard ratios (aHRs) and their 95% confidence intervals (CIs) were determined for each variable [19].

The multivariable model was produced through a backward elimination variable selection model, selecting variables with a P value <.1 in the unadjusted model to be incorporated into the multivariate analysis.

The primary analysis was adjusted with advanced statistical methods, including inverse probability of treatment weighting (IPTW), DOOR analysis, and sensitivity analysis [20–22]. Specific methods are detailed in Supplementary Data 3.

Importantly, the outcome analysis was performed both on the full cohort of patients (model A) and by comparing only VAN/teicoplanin, DAP, and anti-MRSA cephalosporin monotherapy versus anti-MRSA cephalosporins plus DAP combination therapy (model B).

All models were made on real population and on IPTW-adjusted cohort, after balancing the population for all characteristics of patients potentially influencing the treatment assignment, but also variables potentially influencing both the assignment and outcome (confounders).

In all cases, a P value <.05 was considered statistically significant. Statistical analysis was performed using Stata "Standard Edition," version 18.5 software (StataCorp, College Station, TX, USA).

RESULTS

General Characteristics of the Study Population

A total of 465 patients with MRSA-BSI were included: Median age was 76 (IQR, 61–83) years, and 274 (59%) were male. Overall, 50 (11%) patients had endocarditis and 116 (25%) a metastatic disease, while 79 patients had a foreign body infection. The median duration of the bacteremia was 5 (IQR, 3–8) days. At least 1 transthoracic echocardiogram (TTE), transesophageal echocardiogram (TEE), and total body computed tomography (CT) scan was performed in 363 (78%), 74 (16%), and 183 (39%) patients, respectively. At MRSA-BSI onset, the median SOFA score was 2 (IQR, 2–4), and 54 (12%) patients had septic shock, 99 (21%) patients had acute kidney injury, and 131 (28%) had acute respiratory failure.

Antimicrobial Treatment Strategies

All patients received 1 anti-MRSA drug within 24 hours from BSI onset: 255 (55%) received DAP, 149 (32%) received VAN (or teicoplanin), and only 61 (13%) received other in vitro–effective drugs (linezolid, tigecycline, levofloxacin).

Overall, 107 (50 BPR and 57 CPT) anti-MRSA cephalosporins were used, 80 (38 BPR and 42 CPT) of which were used in combination with DAP. The remaining 27 were used in monotherapy (20 cases), 4 cases with linezolid, and 3 with fosfomycin (see detailed description in Supplementary Figure 1).

Of interest, 80 (17%) received initial combination therapy with anti-MRSA cephalosporins plus DAP; Table 1 depicts differences between these patients and those who received OARs.

Patients receiving anti-MRSA cephalosporins plus DAP had lower median age (72 vs 76 years, $P = .01$) and lower median Charlson Comorbidity Index (CCI) score (5 vs 7, $P = .01$), but were more frequently hospitalized in ICU (14% vs 7%, $P = .03$) or affected by a foreign body infection (31% vs 14%, $P < .01$); in addition, SOFA score was higher (3 vs 2, $P = .01$).

The median duration of antibiotic therapy was 21 (IQR, 15–32) days, with no significant differences between the 2 groups ($P = .978$). In depth, the combination therapy of anti-MRSA cephalosporins plus DAP was continued for a median of 10 (IQR, 8–14) days, then 60% of patients were stepped down to monotherapy (65% DAP monotherapy, 35% anti-MRSA cephalosporin).

Primary and Secondary Outcome Analysis

Overall, 181 (39%) patients died within 90 days from MRSA-BSI onset. Table 2 presents primary and secondary outcomes.

The treatment failure of first-line regimen was significantly lower in anti-MRSA cephalosporins plus DAP both in model A and model B. As detailed in Table 2, regarding specific items of composite treatment only, the incidence of persistent MRSA bacteremia was lower in the anti-MRSA cephalosporin plus DAP group. Of note, 6% (27/465) of patients presented the skip phenomenon (intermittent positive blood cultures): 6 (8%) versus 21 (5%) in anti-MRSA cephalosporin plus DAP versus OAR, respectively ($P = .476$).

In Table 3, specific characteristics of patients who survived or did not survive at end of follow-up are reported. Causes of death are reported in Supplementary Table 1.

Survival Analysis

Cox regression model was developed to assess the predictor of 90-day morality (Table 4). The model showed that predictors of mortality were community-acquired MRSA (aHR, 1.86 [95% CI, 1.19–2.88]), CCI score (aHR, 1.16 [95% CI, 1.11–1.22], per 1-point increase), and SOFA score (aHR, 2.17 [95% CI, 1.58–2.97]), while the first-line therapy with anti-MRSA cephalosporins plus DAP combination had a protective effect (aHR, 0.54 [95% CI, .34–.85]).

The model was then adjusted with propensity score (IPTW method). The regimen was still protective both in model A and model B. The impact of this regimen was graphically assessed with Kaplan–Meier curves (Figure 1): Overall, improved survival was noticed in all curves for the anti-MRSA plus DAP group if compared with OAR (model A) or standard monotherapy (model B), even after adjustment with IPTW.

DOOR Analysis

A DOOR analysis was conducted for 90-day composite outcome (Figure 2). Median DOOR score was 3 (IQR, 1–7), significantly lower in anti-MRSA cephalosporins plus DAP arm

Table 1. General Characteristics of Patients Treated With Daptomycin Plus Anti-MRSA Cephalosporins or Other Antibiotic Regimens

Characteristic	Overall (n = 465)	Other Anti-MRSA Regimens (n = 385)	Daptomycin Plus Anti-MRSA Cephalosporins (n = 80)	*P* Value
Age, y, median (IQR)	76 (61–83)	76 (62–84)	72 (52–80)	**.01**
Male sex	274 (59)	222 (58)	52 (65)	.23
Ward of evaluation				
General ward	428 (92)	359 (93)	69 (86)	**.03**
Intensive care unit	37 (8)	26 (7)	11 (14)	
Type of MRSA infection				
Community-acquired	50 (11)	36 (9)	14 (17)	**.03**
Hospital-acquired	415 (89)	349 (91)	66 (83)	
Center of enrollment				
Policlinic of Bologna "Sant'Orsola-Malpighi"	154 (33)	120 (34)	34 (32)	.16
Humanitas IRCCS Hospital—Centro Cardiologico Monzino	119 (26)	84 (24)	35 (33)	
AOU Policlinic of Bari	106 (23)	82 (23)	24 (22)	
Ospedale Vittorio Emanuele II, ASL BT, Bisceglie	86 (18)	72 (20)	14 (13)	
Year of enrollment				
2020–2021	213 (46)	160 (45)	53 (50)	.37
2022–2024	252 (54)	198 (55)	54 (50)	
CCI score, median (IQR)	7 (4–8)	7 (5–8)	5 (3–8)	**.01**
Concurrent SARS-CoV-2 infection	40 (13)	27 (12)	13 (18)	.39
Comorbidity				
Cardiovascular disease	110 (24)	91 (24)	19 (24)	.98
Chronic obstructive pulmonary disease	97 (21)	84 (22)	13 (16)	.26
Type 2 diabetes	161 (35)	85 (22)	19 (24)	.74
Chronic kidney disease (eGFR <60 mL/min)	104 (22)	127 (33)	34 (42)	.10
Obesity (BMI >30 kg/m^2)	53 (17)	39 (16)	14 (18)	.71
Solid neoplasia	90 (19)	74 (19)	16 (20)	.88
Hematologic neoplasia	26 (6)	19 (5)	7 (9)	.17
Other immunosuppressive diseases	39 (8)	29 (8)	10 (12)	.14
Intravenous drug use	9 (2)	5 (1)	4 (5)	**.02**
Endocarditis[a]	50 (11)	38 (10)	12 (15)	.17
Metastatic disease	116 (25)	90 (24)	26 (32)	.08
Lung metastatic foci	39 (8)	26 (7)	13 (16)	**.01**
CNS metastatic foci	7 (2)	6 (2)	1 (1)	.83
Spondylodiscitis	37 (8)	26 (7)	11 (14)	**.03**
Other (skin and soft tissue, kidney, spleen)	33 (7)	26 (7)	7 (9)	.40
Presence of foreign body infection	79 (17)	54 (14)	25 (31)	**<.01**
Instrumental diagnostic				
TTE and TEE	363 (78)	290 (75)	73 (91)	**.01**
Only TEE	74 (16)	52 (14)	22 (28)	**.01**
Total body CT	183 (39)	141 (37)	42 (53)	**.01**
Deep site infections with possible source control	93 (20)	62 (16)	31 (38)	**<.01**
Adequate source control achieved within 72 h of therapy	67 (72)	45 (72)	19 (61)	.26
Duration of MRSA-BSI, d, median (IQR)	5 (3–8)	5 (4–8)	4 (2–7)	**.01**
SOFA score at presentation, median (IQR)	2 (2–4)	2 (2–4)	3 (2–5)	**.01**
Septic shock at presentation	54 (12)	41 (11)	13 (16)	.15
Acute kidney injury at presentation	99 (21)	79 (21)	20 (25)	.37
Acute respiratory failure at presentation	131 (28)	105 (27)	26 (32)	.34
Thrombocytopenia	77 (17)	59 (15)	18 (22)	.11
Infectious diseases evaluations, No., median (IQR)	3 (2–4)	3 (2–4)	3 (3–4)	.32
Use of anti-MRSA cephalosporins	107 (23)	27 (7)	80 (100)	**<.01**
Duration of antibiotic therapy, d, median (IQR)	21 (15–32)	21 (15–28)	21 (11–31)	.97

Data are presented as No. (%) unless otherwise indicated. Bold values indicate statistically significant results.

Abbreviations: AOU, Azienda Ospedaliera Universitaria, University Hospital; ASL BT, Azienda Sanitaria Locale Barletta-Andria-Trani, Hospital of Barletta-Andia-Trani; BMI, body mass index; CCI, Charlson Comorbidity Index; CNS, central nervous system; CT, computed tomography; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, Sequential Organ Failure Assessment; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]Among endocarditis, 3 cases were both right-sided and left-sided endocarditis.

Table 2. Primary and Secondary Outcomes Analysis

Outcome	Overall (n = 465)	Model A: Full Cohort			Model B: Combination vs Standard Monotherapy[a]		
		Other Anti-MRSA Regimens (n = 385)	DAP + Anti-MRSA Cephalosporins (n = 80)	*P* Value	Standard Monotherapy[a] (n = 303)	DAP + Anti-MRSA Cephalosporins (n = 80)	*P* Value
30-d mortality	151 (32)	132 (34)	19 (24)	.06	104 (34)	19 (24)	.07
90-d mortality	182 (39)	159 (41)	23 (29)	**.03**	125 (41)	23 (29)	**.04**
Treatment failure	260 (56)	226 (59)	34 (42)	**.01**	175 (58)	34 (42)	**.01**
Persistent bacteremia >5 d	185 (40)	162 (42)	23 (29)	**.02**	127 (42)	23 (29)	**.03**
Persistent signs of MRSA infection or ICU admission after at least 7 d of effective treatment	138 (30)	120 (31)	18 (22)	.12	96 (32)	18 (22)	.11
Newly identified metastatic focus of infection after at least 72 h of effective treatment	36 (8)	29 (8)	4 (5)	.42	26 (9)	4 (5)	.28
Treatment discontinuation for any cause	61 (13)	51 (13)	10 (12)	.85	42 (14)	10 (12)	.75
90-d MRSA-BSI relapse	27 (6)	24 (6)	3 (4)	.38	21 (7)	3 (4)	.29
Duration of MRSA-BSI, d, median (IQR) (n = 452)	5 (3–8)	5 (4–8)	4 (2–7)	**.01**	5 (4–8)	4 (2–7)	**.01**
Serious adverse events leading to antibiotic therapy discontinuation	39 (9)	31 (8)	8 (10)	.56	21 (7)	8 (10)	.35
Incidence of *Clostridioides difficile* colitis	12 (3)	10 (3)	2 (2)	.96	8 (3)	2 (2)	.94
Duration of hospitalization, d, median (IQR)	20 (12–34)	19 (12–32)	23 (14–39)	**.03**	19 (12–34)	23 (14–39)	**.03**

Data are presented as No. (%) unless otherwise indicated. Bold values indicate statistically significant results.

Abbreviations: BSI, bloodstream infection; DAP, daptomycin; ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Standard monotherapy: 144 vancomycin, 5 teicoplanin, 134 daptomycin, 20 anti-MRSA cephalosporins.

(2 [IQR, 1–7] vs 3 [IQR, 1–7]; $P = .003$). Patients in the anti-MRSA cephalosporins plus DAP arm had a 59.9% (95% CI, 52.4%–67.4%, $P = .01$) probability of having a better outcome than those in the OAR arm. Importantly, the analysis showed that patients treated with anti-MRSA cephalosporins plus DAP reached a recovery without complications in 46% of cases if compared to 28% in the OAR group. Core components of DOOR analysis are presented in Supplementary Table 2 and Supplementary Figure 2.

Subgroup Analysis

The IPTW-adjusted cohort was used to explore potential benefit of anti-MRSA cephalosporins plus DAP on 90-day mortality risk on prespecified subgroups: The model showed a reduced risk in patients in the general ward (−15%), with metastatic disease (−25%), prosthetic device infection (−29%), septic shock (−43%), or acute respiratory failure (−25%) (Figure 3).

DISCUSSION

Optimal treatment of MRSA-BSI is still debated within the infectious diseases community, as stated in expert opinions exploring this topic [10, 16]; this reflects the paucity of high-quality data and the absence of an international standard of care for the management of MRSA-BSI.

This study evaluated effectiveness and safety of anti-MRSA cephalosporins plus DAP as initial treatment strategy, if compared with other anti-MRSA regimens, using a detailed outcomes analysis including DOOR, IPTW adjustment, and subgroup treatment effect, in a large multicentric cohort of patients.

The novelty of this analysis is represented by the investigation of this combination since the very early days of BSI, while smaller previous studies [12–16] explored the effectiveness of combining daptomycin with CPT/BPR as salvage therapy for MRSA-BSI. For instance, one of the most important retrospective studies on 60 patients evaluated DAP + CPT versus standard of care as salvage therapy. DAP + CPT was associated with a numerically lower incidence of clinical failure (20% vs 43%; $P = .052$), and after adjusting for baseline differences, DAP + CPT was associated with a 77% reduction in the odds of clinical failure [14]. However, this experience was limited by the low sample size and the use of combination as salvage therapy. Similarly, the single clinical trial on this topic, showing a potential superiority of initial DAP + CPT therapy, was concluded early for ethical concerns [13]. Of note, despite that the data appear intriguing when DAP is part of combination therapy, studies involving VAN as a companion drug of anti-MRSA cephalosporins led to opposite results: A recent multicentric study [23] performed a comparative analysis of anti-MRSA

Table 3. Characteristics of Patients Who Survived or Did Not Survive to Day 90 After MRSA-BSI Onset

Characteristic	Overall (n = 465)	90-d Survivors (n = 283)	90-d Nonsurvivors (n = 181)	*P* Value
Age, y, median (IQR)	76 (61–83)	67 (56–80)	80 (74–86)	**<.01**
Male sex	274 (59)	169 (60)	105 (58)	.71
Ward of evaluation				
General ward	428 (92)	262 (93)	166 (91)	.59
Intensive care unit	37 (8)	21 (7)	16 (9)	
Type of MRSA infection				
Community-acquired	50 (11)	24 (8)	26 (14)	**.04**
Hospital-acquired	415 (89)	259 (92)	156 (86)	
Center of enrollment				
Policlinic of Bologna "Sant'Orsola-Malpighi"	154 (33)	94 (33)	60 (33)	.98
Humanitas IRCCS Hospital–Centro Cardiologico Monzino	119 (26)	74 (26)	45 (25)	
AOU Policlinic of Bari	106 (23)	63 (22)	43 (24)	
Ospedale Vittorio Emanuele II, ASL BT, Bisceglie	86 (18)	52 (18)	34 (19)	
Year of enrollment				
2020–2021	213 (46)	127 (45)	86 (47)	.61
2022–2024	252 (54)	156 (55)	96 (53)	
CCI score, median (IQR)	7 (4–8)	6 (3–8)	7 (6–9)	**<.01**
Concurrent SARS-CoV-2 infection	40 (13)	20 (11)	20 (17)	.06
Comorbidity				
Cardiovascular disease	110 (24)	57 (20)	53 (29)	**.02**
Chronic obstructive pulmonary disease	97 (21)	52 (18)	45 (25)	.10
Type 2 diabetes	161 (35)	59 (21)	45 (25)	.32
Chronic kidney disease (eGFR <60 mL/min)	104 (22)	88 (31)	73 (40)	**.04**
Obesity (BMI >30 kg/m^2)	53 (17)	32 (16)	21 (17)	.84
Solid neoplasia	90 (19)	48 (17)	42 (23)	.10
Hematologic neoplasia	26 (6)	13 (5)	13 (7)	.24
Other immunosuppressive disease	39 (8)	27 (10)	12 (7)	.26
Intravenous drug use	9 (2)	6 (2)	3 (2)	.71
Endocarditis[a]	50 (11)	26 (9)	24 (13)	.17
Metastatic disease, at least 2 foci	116 (25)	66 (23)	50 (27)	.31
Lung metastatic foci	39 (8)	21 (7)	18 (10)	.34
CNS metastatic foci	7 (2)	1 (<1)	6 (3)	**.01**
Spondylodiscitis	37 (8)	22 (8)	15 (8)	.85
Other (skin and soft tissue, kidney, spleen)	33 (7)	21 (7)	12 (7)	.74
Presence of foreign body infection	79 (17)	41 (14)	38 (21)	.07
Instrumental diagnostic				
TTE and TEE	363 (78)	245 (87)	118 (65)	**<.01**
Only TEE	74 (16)	56 (20)	18 (10)	**.01**
Total body CT	183 (39)	120 (43)	63 (35)	.08
Deep site infections with possible source control	93 (20)	53 (19)	40 (22)	.37
Adequate source control achieved within 72 h of therapy	67 (72)	38 (71)	29 (72)	.93
Duration of MRSA-BSI, d, median (IQR)	5 (3–8)	2 (1–4)	3 (2–6)	**<.01**
SOFA score at presentation, median (IQR)	2 (2–4)	5 (3–7)	5 (4–9)	**<.01**
Septic shock at presentation	54 (12)	25 (9)	29 (16)	**.02**
Acute kidney injury at presentation	99 (21)	45 (16)	54 (30)	**<.01**
Acute respiratory failure at presentation	131 (28)	63 (22)	68 (37)	**<.01**
Thrombocytopenia	77 (17)	32 (11)	45 (25)	**<.01**
Type of antibiotic therapy				
Vancomycin/teicoplanin	149 (32)	85 (30)	64 (35)	**.01**
Daptomycin	255 (55)	171 (60)	84 (46)	
Other drugs (linezolid, tigecycline, levofloxacin)	61 (13)	27 (10)	34 (19)	
Use of anti-MRSA cephalosporins	107 (23)	64 (23)	43 (24)	
Infectious diseases evaluations, No., median (IQR)	3 (2–4)	3 (3–4)	3 (2–4)	.67
Incidence of treatment failure	260 (56)	134 (47)	126 (69)	**<.01**

Table 3. Continued

Characteristic	Overall (n = 465)	90-d Survivors (n = 283)	90-d Nonsurvivors (n = 181)	*P* Value
Serious adverse events to antibiotic therapy	39 (8)	20 (7)	19 (11)	.20
Duration of antibiotic therapy, d, median (IQR)	21 (15–32)	21 (14–28)	22 (17–30)	.87

Data are presented as No. (%) unless otherwise indicated. Bold values indicate statistically significant results.

Abbreviations: AOU, Azienda Ospedaliera Universitaria, University Hospital; ASL BT, Azienda Sanitaria Locale Barletta-Andria-Trani, Hospital of Barletta-Andia-Trani; BMI, body mass index; BSI, bloodstream infection; CCI, Charlson Comorbidity Index; CNS, central nervous system; CT, computed tomography; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, Sequential Organ Failure Assessment; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]Among endocarditis, 3 cases were both right-sided and left-sided endocarditis.

cephalosporin combination therapy versus monotherapy, which failed to demonstrate any benefit of this combination. However, some important concerns should be noted: First, the study of Hicks et al [23] assessed the effectiveness of VAN plus CPT, and only 3 DAP-based combinations were present; second, the study demonstrated a very low mortality rate (almost one-half that of our series), especially in the monotherapy group (30-day mortality of 18%); this suggests that the group of "high-risk patients" was small and most likely assigned to combination therapy, hampering comparison.

This leads to another important element of discussion. Although data are not definitive and large heterogeneity still exists in preferring DAP or VAN as the regimen of choice for MRSA-BSI [24], in centers included in this study a predominant use of DAP as MRSA treatment (including early combination therapy) can be evidenced; these institutions concluded that the benefit of DAP over VAN may be superior to higher antibiotic cost. Similarly, given the potential complications of uncontrolled MRSA infection, the use of early combination therapies is also considered acceptable.

Another important element of this analysis is the population of patients, representing a reliable "real-world" collection of cases of MRSA-BSI.

The median age was 10–15 years older and CCI score 2 points higher than in similar studies on MRSA [10–16, 23]. This is not uncommon in Italian hospitals and is associated with the generally older and comorbid population; this explains the variety of MRSA-associated clinical syndromes, including severe infections with a SOFA score higher the usual (2 points), multiple metastatic foci, endocarditis, and foreign body infections. In turn, the 90-day mortality and the treatment failure are quite high (39% and 56%, respectively); however, as presented in the supplementary tables, most of the deaths were directly attributable to the infection.

In this complex scenario of MRSA-BSIs, the major association found with the use of anti-MRSA cephalosporins plus DAP was on duration of bacteremia: Patients exposed to this combination had a shorter duration of BSI (a median of 1 day less) and a lower incidence of cases of persistent bacteremia (≥5 days), if compared with other regimens. Furthermore, also a significantly lower incidence of 90-day mortality rate was noticed; it is reasonable to think that the more potent in vitro activity of combination therapy [25] may contribute to a more rapid bacterial clearance and a lower likelihood of persistent infection, lowering the overall risk of 90-day mortality. This result was confirmed in the multivariable Cox regression model, even after IPTW adjustment, addressing potential confounding biases of therapy allocation.

Finally, 30-day mortality, persistent clinical signs of MRSA infection, and incidence of newly identified metastatic foci of infection were numerically lower in the anti-MRSA cephalosporins plus DAP group, but did not reach statistical significance.

Data were confirmed by advanced statistical approaches. The DOOR analysis showed that the use of anti-MRSA cephalosporins plus DAP was associated with a higher likelihood of achieving a more desirable outcome, such as a higher rate of recovery without complications and reduced treatment failure. These outcomes were in line with the DOOR approach [17, 18], prioritizing not only survival but also the absence of post-treatment complications, which are crucial in managing high-risk populations with MRSA-BSI.

On the other hand, the subgroup analyses on IPTW-adjusted population showed that the combination therapy probably is worthy in specific MRSA-associated clinical syndromes, including disseminated and metastatic infections, prosthetic device infections, and critical illness causing septic shock or acute respiratory failure. This is consistent with studies showing how MRSA-BSI can be associated with different clinical phenotypes with consistent differences in outcomes [26], highlighting the need for tailored therapeutic strategies for each of these conditions. This can be a possible explanation of conflicting results regarding the beneficial effect of shortening the duration of BSI in different studies: The survival benefit may be more pronounced if some specific clinical scenarios are well represented in the study population.

Aside from the debate regarding the higher effectiveness of a synergistic combination therapy over monotherapy [27], an important concern is whether a theoretically more effective treatment should be initiated in "high-risk" patients, including those with persistent bacteremia, endocarditis, or BSIs associated with severe clinical conditions.

Table 4. Univariate and Multivariate Cox Regression Model for Predictors of 90-Day Mortality

				Model A: Full Cohort						Model B: Combination vs Standard of Care					
	Univariate Analysis			Multivariate Analysis			IPTW-Adjusted Multivariate Analysis			Multivariate Analysis			IPTW-Adjusted Multivariate Analysis		
Predictors of 90-d Mortality	HR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value
Age, per 1-y increase	1.05	(1.03–1.06)	**<.001**	…[a]	…		…[a]	…		…[a]	…		…[a]	…	
Male sex	0.91	(.68–1.23)	.576	0.83	(.61–1.12)	.235	0.77	(.52–1.15)	.212	0.84	(.60–1.18)	.339	0.83	(.53–1.30)	.420
Intensive care unit admission	1.17	(.70–1.96)	.531	…	…		…	…		…	…		…	…	
Community-acquired MRSA (vs hospital-acquired)	1.44	(.95–2.19)	.085	1.86	(1.19–2.88)	**.006**	2.47	(1.56–3.91)	**<.001**	2.13	(1.35–3.34)	**.001**	2.70	(1.69–4.32)	**<.001**
Center of enrollment															
Policlinic of Bologna "Sant'Orsola-Malpighi"	1	…		…	…		…	…		…	…		…	…	
Humanitas IRCCS Hospital-Centro Cardiologico Monzino	0.83	(.56–1.23)	.371	…	…		…	…		…	…		…	…	
AOU Policlinic of Bari	1.04	(.70–1.55)	.819	…	…		…	…		…	…		…	…	
Ospedale Vittorio Emanuele II, ASL BT, Bisceglie	0.92	(.61–1.43)	.766	…	…		…	…		…	…		…	…	
Year of enrollment															
2020–2021	1	…		1	…		1			1			1		
2022–2024	0.92	(.68–1.23)	.578	0.95	(.71–1.29)	.774	1.10	(.75–1.61)	.624	0.97	(.70–1.36)	.895	1.05	(.69–1.59)	.813
CCI score, per 1 point increase	1.15	(1.10–1.20)	**<.001**	1.16	(1.11–1.22)	**<.001**	1.21	(1.14–1.29)	**<.001**	1.13	(1.08–1.19)	**.001**	1.18	(1.11–1.26)	**<.001**
Intravenous drug use	0.73	(.23–2.31)	.601	…	…		…	…							
Endocarditis	1.27	(.83–1.96)	.262	…	…		…	…		…	…		…	…	
Metastatic disease	0.78	(.56–1.10)	.163	…	…		…	…		…	…		…	…	
High-risk sites of infection (vs low risk)	1.20	(.84–1.71)	.308	0.98	(.76–1.42)	.923	1.27	(.84–1.92)	.255	0.99	(.66–1.48)	.965	1.27	(.82–2.00)	.282
Presence of foreign body infection	1.24	(.86–1.77)	.238	…	…		…	…		…	…		…	…	
Instrumental diagnostic															
TTE	0.28	(.20–.38)	**<.001**	…	…		…	…		…	…		…	…	
Total body CT	0.57	(.42–.78)	**<.001**	…	…		…	…		…	…		…	…	
SOFA score (>4 points)	1.80	(1.32–2.44)	**<.001**	2.17	(1.58–2.97)	**<.001**	2.83	(1.90–4.23)	**<.001**	2.40	(1.68–3.43)	**<.001**	3.08	(1.96–4.86)	**<.001**
Septic shock at presentation	1.76	(1.18–2.62)	**.005**	…[b]	…		…[b]	…		…[b]	…		…[b]	…	
Acute kidney injury at presentation	1.57	(1.14–2.16)	**.005**	…[b]	…		…[b]	…		…[b]	…		…[b]	…	
Acute respiratory failure at presentation	1.41	(1.05–1.91)	**.023**	…[b]	…		…[b]	…		…[b]	…		…[b]	…	
Thrombocytopenia	1.81	(1.29–2.53)	**.001**	…[b]	…		…[b]	…		…[b]	…		…[b]	…	
Antibiotic therapy															
Monotherapy	1	…		…	…		…	…		…	…		…	…	
Combination therapy	0.67	(.49–.90)	**.009**	…	…		…	…		…	…		…	…	
Backbone of antibiotic therapy															
Vancomycin/teicoplanin	1	…		…	…		…	…		…	…		…	…	
Daptomycin	0.60	(.43–.83)	**.003**	…	…		…	…		…	…		…	…	
Other drugs	1.22	(.80–1.85)	.344	…	…		…	…		…	…		…	…	
Type of combination therapy															
Monotherapy	1	…		…[c]	…		…[c]	…		…[c]	…		…[c]	…	
Daptomycin plus β-lactams	0.62	(.45–.85)	**.004**	…[c]	…		…[c]	…		…[c]	…		…[c]	…	
Fosfomycin plus anti-MRSA drug	1.06	(.39–2.88)	.909	…[c]	…		…[c]	…		…[c]	…		…[c]	…	

Table 4. Continued

	Model A: Full Cohort								Model B: Combination vs Standard of Care					
	Univariate Analysis			Multivariate Analysis			IPTW-Adjusted Multivariate Analysis			Multivariate Analysis			IPTW-Adjusted Multivariate Analysis	
Predictors of 90-d Mortality	HR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value	aHR	(95% CI)	*P* Value
Other combinations of anti-MRSA drugs	0.91	(.40–2.09)	.842	…[c]	…		…[c]	…		…[c]	…		…[c]	…	
Use of fifth-generation cephalosporins	0.89	(.63–1.26)	.533	…	…		…	…		…	…		…	…	
Daptomycin plus anti-MRSA cephalosporins	0.57	(.36–.88)	**.013**	0.54	(.34–.85)	**.009**	0.44	(.26–.77)	**.004**	0.51	(.32–.81)	**.005**	0.42	(.25–.73)	**.002**

Model B, standard monotherapy: 144 vancomycin, 5 teicoplanin, 134 daptomycin, 20 anti-MRSA cephalosporins. Bold values indicate statistically significant results.

Abbreviations: aHR, adjusted hazard ratio; AOU, Azienda Ospedaliera Universitaria, University Hospital; ASL BT, Azienda Sanitaria Locale Barletta-Andria-Trani, Hospital of Barletta-Andia-Trani; CCI, Charlson Comorbidity Index; CI, confidence interval; CT, computed tomography; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MRSA, methicillin-resistant *Staphylococcus aureus*; SOFA, Sequential Organ Failure Assessment; TTE, transthoracic echocardiography.

[a]Removed for collinearity with CCI score.

[b]Removed for collinearity with SOFA score.

[c]Removed for collinearity between "Daptomycin plus β-lactams" and "Daptomycin plus fifth-generation cephalosporins."

Accordingly, it should be noted that the median duration of bacteremia presented in this study is in line with recent trials [11] and multicentric studies [12] including MRSA-BSI; hence, the median reduction of at least 1 day of bacteremia should be considered particularly significant, also considering that in this study patients in the anti-MRSA cephalosporins plus DAP group received less frequently a timely source control. In addition, despite being outside the aims of the study, data showed a median duration of therapy of 3–4 weeks, which is shorter than usually recommended. This follows the idea of a personalized treatment approach to *S. aureus* BSI: Especially when the infection is quickly controlled, the duration of therapy may be safely reduced.

Data from this study support the "hit hard and hit fast" strategy for patients with complex conditions, since they can obtain the highest beneficial effect from this approach, with a higher likelihood of treatment success and clearance of the bacteremia, and reduce the risk of complications (leading to long-term mortality).

Of note, in this study there was a similar incidence of adverse events between the anti-MRSA cephalosporins plus DAP combination and OARs; this is in contrast with data deriving from CAMERA-2 trial [28], but it is probably explainable by the prevalence of VAN plus piperacillin-tazobactam (or flucloxacillin) combination in the cited trial, which is known for its nephrotoxic risk [29, 30], along with specific characteristics of the study population and the relatively high VAN area under the concentration–time curve documented in the study [30]. On the contrary, anti-MRSA cephalosporins plus DAP are not supposed to be more nephrotoxic than other regimens, as reported in this study.

Nevertheless, the hypothesis of the use of this combination as initial strategy, followed by a quick de-escalation to monotherapy with DAP, an anti-MRSA cephalosporin, or another anti-MRSA drug after the achievement of negative blood cultures and clinical stability, is likely very attractive; in fact, previous data support this approach without increase in the risk of adverse outcomes [31].

Despite the promising results, several limitations must be acknowledged. This study was retrospective, and while IPTW was applied to reduce bias, residual confounding cannot be excluded. Importantly, the study was conducted during the COVID-19 pandemic and over 4 different hospitals, which can still be a risk for additional biases, albeit specific adjustment for these variables resulted not significant.

Additionally, the comparator group in our study was heterogeneous, including various anti-MRSA regimens, which may have influenced the outcomes. The relatively small sample size in the anti-MRSA cephalosporins plus DAP group compared to OARs also warrants further investigation in larger, prospective interventional studies to validate these findings. Similarly, the comparison between CPT and BPR

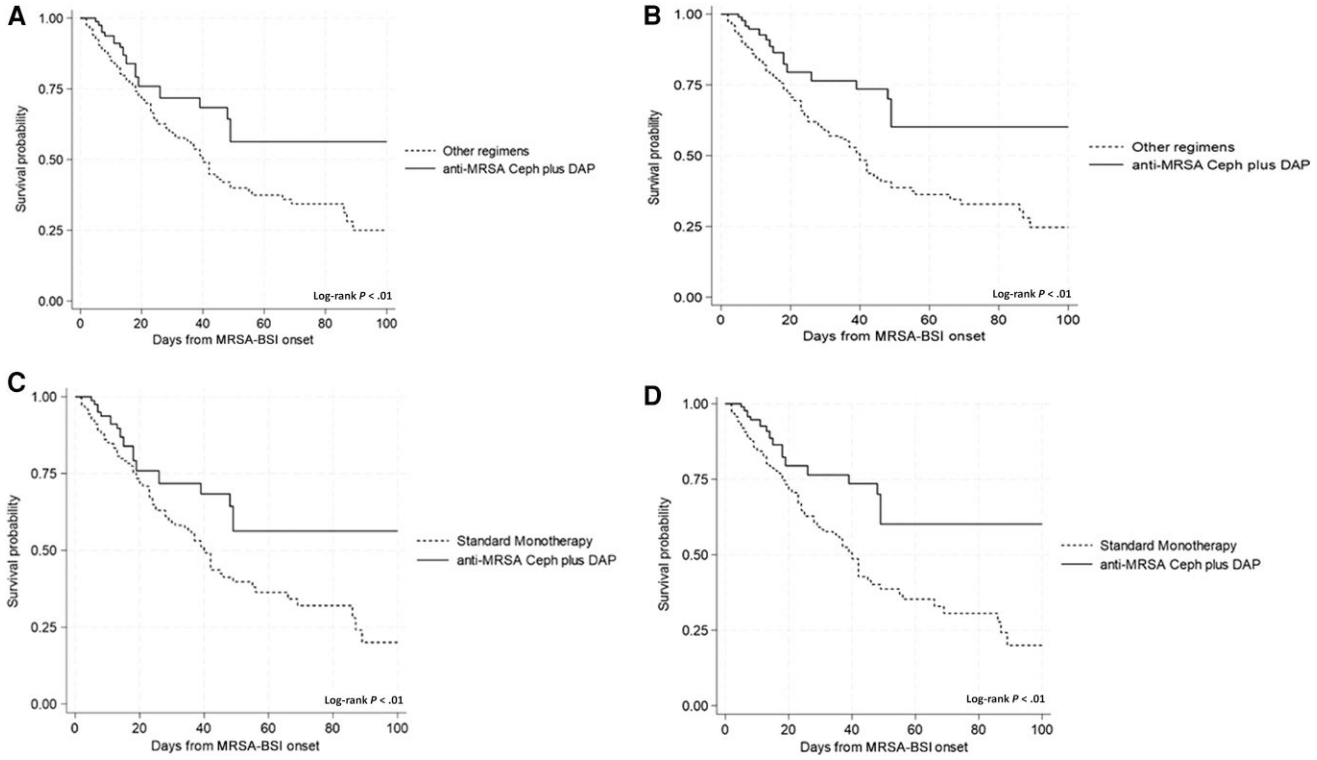

Figure 1 Kaplan–Meier curves. *A*, Model A, unadjusted cohort. *B*, Model A, IPTW-adjusted cohort. *C*, Model B, unadjusted cohort. *D*, Model B, IPTW-adjusted cohort. Abbreviations: BSI, bloodstream infection; Ceph, cephalosporin; DAP, daptomycin; IPTW, inverse probability of treatment weighting; MRSA, methicillin-resistant *Staphylococcus aureus*.

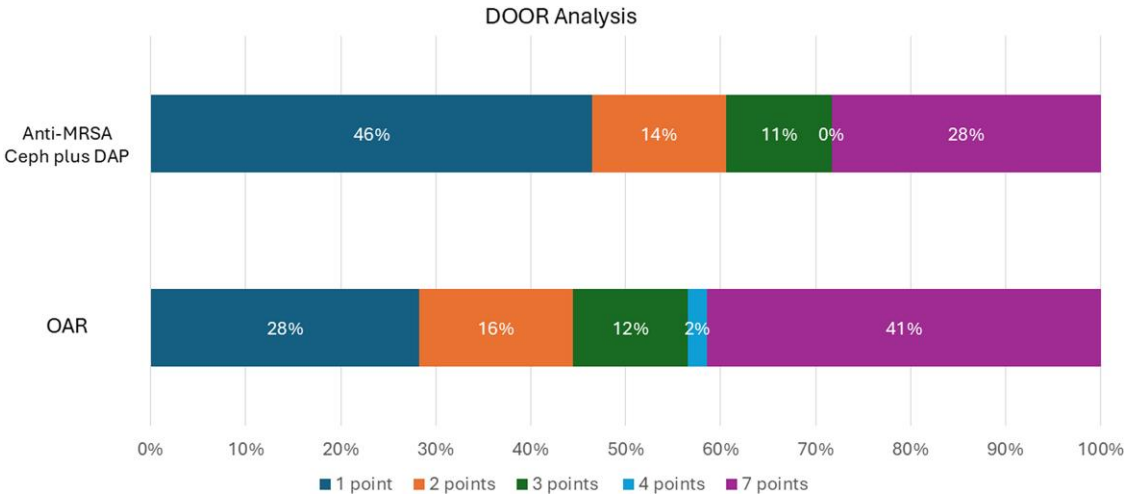

Figure 2. DOOR analysis. Abbreviations: Ceph, cephalosporin; DAP, daptomycin; DOOR, desirability of outcome ranking; MRSA, methicillin-resistant *Staphylococcus aureus*; OAR, other antibiotic regimen.

warrants further evaluation, as well as the comparison of anti-MRSA cephalosporins plus DAP versus other highly performant combinations, such as DAP plus fosfomycin. Finally, the association between in vitro synergy (demonstrated for each strain) and clinical outcomes is still unclear: It can be assumed that the effectiveness of this strategy may be different according to the phenotypic and genotypic profile of each strain [32].

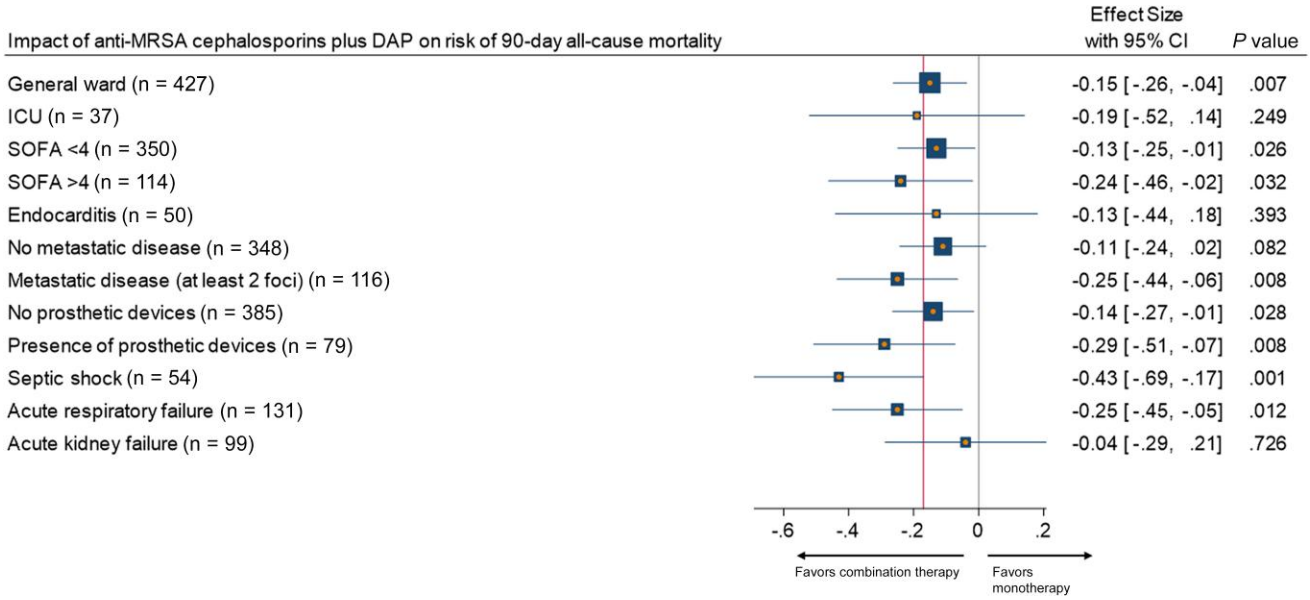

Figure 3. Forest plot of the effect of anti-MRSA cephalosporins plus DAP on 90-day all-cause mortality in prespecified subgroups (IPTW-adjusted cohort). Abbreviations: CI, confidence interval; DAP, daptomycin; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; MRSA, methicillin-resistant *Staphylococcus aureus*; SOFA, Sequential Organ Failure Assessment.

In conclusion, this study provides newer data supporting the use of anti-MRSA cephalosporins plus DAP as first-line therapy for MRSA-BSI, which was associated with lower mortality and treatment failure rates compared to other regimens in this large retrospective study. Despite the limitations of this trial, evidence is mounting that the "hit hard and hit fast" initial strategy may be valuable in cases of MRSA bacteremia, particularly in high-risk settings.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. D. F. B. and A. B. were responsible for the study design. D. F. B. performed data cleaning, visualization, and statistical analysis. A. B. drafted the first version of the manuscript. D. F. B. and M. B. directly accessed and verified the underlying data reported in the manuscript. All other authors contributed to data collection and carefully read and commented on the manuscript. All authors had final responsibility for the decision to submit for publication.

Data availability. The dataset is available from the corresponding author upon reasonable request.

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